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ATTORNEY'S DOCKET NUMBER: HM/2-21848/A/PCT

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/806844

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP 99/07313	October 2, 1999	~~October 9, 2001~~ October 9, 1998

TITLE OF INVENTION
HYDROXYSTILBENE COMPOUNDS USED AS MICROBICIDAL ACTIVE SUBSTANCES

APPLICANT(S) FOR DO/EO/US
Werner Hölzl, Dietmar Ochs, Wolfgang Haap, Karin Puchtler and Marcel Schnyder

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☑ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☑ has been transmitted by the International Bureau. **(See attached Form PCT/IB/308)**
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☑ A translation of the International Application into English 35.U.S.C. 371(c)(2)).
7. ☑ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C.371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☑ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☑ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included.

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☑ **A FIRST preliminary amendment.**
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☑ Other items or information: **(See attached Form PCT/ISA/210)**

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/806844	PCT/EP 99/07313	HM/2-21848/A/PCT

17. ☑ The following fees are submitted:		CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)):	**$860.00**	
Search Report has been prepared by the EPO or JPO	$860.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482)	$690.00	
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	$750.00	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$1000.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		**$860.00**
Surcharge of **$130.00** for furnishing the oath of declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	17 - 20 =	0	X **$18.00**	$
Independent claims	2 -3 =	0	X **$80.00**	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$
TOTAL OF ABOVE CALCULATIONS =				**$860.00**
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$
SUBTOTAL =				**$860.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$
TOTAL NATIONAL FEE =				**$860.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$
TOTAL FEES ENCLOSED =				$
			Amount to be: refunded	$
			charged	**$860.00**

a. ☑ Please charge my Deposit Account No. 03-1935 in the amount of **$860.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

b. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 03-1935. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

PLEASE ASSOCIATE THE ATTACHED APPLICATION WITH **CUSTOMER NUMBER 000324** AND SEND ALL CORRESPONDENCE TO:

JoAnn Villamizar, Ciba Specialty Chemicals Corporation
Patent Department
540 White Plains Road
P.O. Box 2005
Tarrytown, NY 10591-9005

DATE: April 5, 2001

Kevin T. Mansfield
SIGNATURE

Kevin T. Mansfield, Agent for Applicants
NAME

31,635
REGISTRATION NUMBER

CASE HM/2-21848/A/PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
WERNER HÖLZL ET AL.
INTERNATIONAL APPLICATION NO. PCT/EP EP 99/07313
FILED: OCTOBER 2, 1999
FOR: HYDROXYSTILBENE COMPOUNDS USED AS MICROBICIDAL ACTIVE SUBSTANCES
U.S. APPLICATION NO: UNASSIGNED
35 USC 371 DATE:

Group Art Unit: unassigned
Examiner: unassigned

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

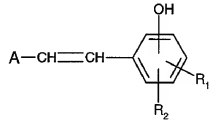
Sir:

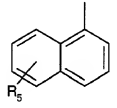
Kindly amend this application as follows prior to calculation of the filing fee and consideration on the merits.

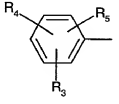
Please cancel claims 1-15.

Please add claims 18-32.

--18. (new) A method of antimicrobially treating a substrate, which comprises applying thereto an antimicrobially effective amount of a hydroxystilbene compound of the formula

(1)  , wherein

A is a radical of formula (1a)  ; or a radical of

formula (1b)  ; and

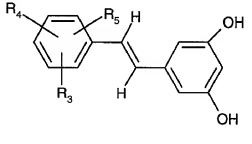
R_1, R_2, R_3, R_4 and R_5 are each independently of the others hydrogen, halogen, hydroxy, C_1-C_{16}alkyl, C_1-C_{16}alkoxy, phenyl; C_1-C_3phenylalkyl; C_6-C_{10}aryloxy, amino, mono-C_1-C_5alkylamino, di-C_1-C_5alkylamino, or -NO_2.

19. (new) A method according to claim 18, wherein, in formula (1), R_1 and R_2 are hydroxy.

20. (new) A method according to claim 18, wherein the compound of formula (1) is in the E- or Z-form.

21. (new) A method according to claim 20, wherein the compound of formula (1) is in the E-form.

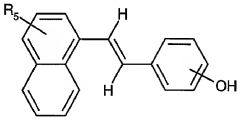
22. (new) A method according to claim 18, wherein there is used a compound of formula

(2) 

wherein R_3, R_4 and R_5 are as defined in claim 18.

23. (new) A method according to claim 22, wherein, in formula (2), R_3, R_4 and R_5 are hydrogen.

24. (new) A method according to claim 18, wherein there is used a compound of formula

(3) 

wherein R_5 is as defined in claim 18.

25. (new) A method of antimicrobial treatment, deodorisation and disinfection of the skin, mucosa and hair treating, which comprises applying thereto an antimicrobially effective amount of a compound of formula (1) according to claim 18.

26. (new) A method according to claim 25, wherein the compound of formula (1) is used in disinfection and deodorisation.

27. (new) A method of antimicrobially treating textile fibre materials, which comprises applying thereto an antimicrobially effective amount of a hydroxystilbene compound of the formula (1) according to claim 18.

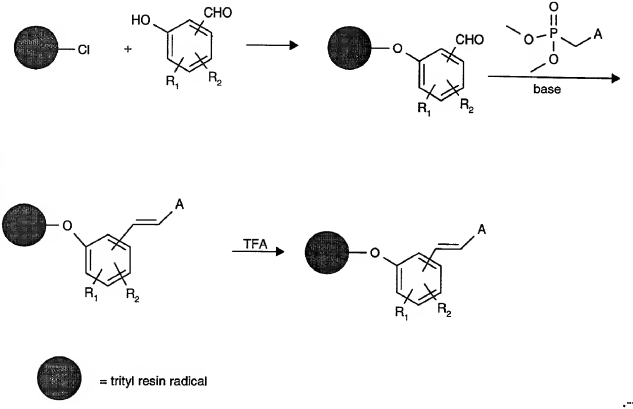
28. (new) A method of preserving a substrate against antimicrobial damage, which comprises applying thereto an antimicrobially effective amount of a hydroxystilbene compound of the formula (1) according to claim 18.

29. (new) A method of washing and cleaning a substrate, which comprises washing and cleaning the substrate with a washing and cleaning formulation containing an antimicrobially effective amount of a hydroxystilbene compound of the formula (1) according to claim 18.

30. (new) A method of imparting antimicrobial properties to and preserving plastics, paper, nonwovens, wood or leather, which comprises applying thereto an antimicrobially effective amount of a hydroxystilbene compound of the formula (1) according to claim 18.

31. (new) A personal care preparation, comprising from 0.01 to 15 % by weight, based on the total weight of the composition, of a compound of formula (1) according to claim 18, and a cosmetically tolerable adjuvant.

32. (new) A process for the preparation of compounds of formula (1) according to claim 18, which process comprises preparing them in a solid-phase synthesis using a trityl resin in accordance with the following scheme:



REMARKS

Claims 16-32 are pending.

Applicants present claims 16-17 and a clean set of claims 18-32, corresponding to claims 1-15, to eliminate informal "use of" claims and/or multiple dependency and to make minor editorial changes. Said claims are supported by original claims 1-15 and the corresponding disclosure. No new matter has been added.

Applicants aver that the claims are now in better form for examination. An Action on the merits of the claims is respectfully awaited.

Respectfully submitted,

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Agent for Applicants
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KTM\21848PA

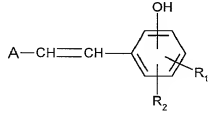
APR 05 2001

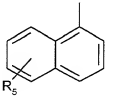
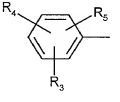
09/806844
JC08 Rec'd PCT/PTO 05 APR 2001

Hydroxystilbene compounds used as microbicidal active substances

The present invention relates to the use of hydroxystilbene compounds in the antimicrobial treatment of surfaces.

The hydroxystilbene compounds used according to the invention correspond to formula

(1)  , wherein

A is a radical of formula (1a)  ; or a radical of formula (1b)  ; and

R_1, R_2, R_3, R_4 and R_5 are each independently of the others hydrogen, halogen, hydroxy, C_1-C_{16}alkyl, C_1-C_{16}alkoxy, phenyl; C_1-C_3phenylalkyl; C_6-C_{10}aryloxy, amino, mono-C_1-C_5alkylamino, di-C_1-C_5alkylamino, or $-NO_2$.

C_1-C_{16}Alkyl are straight-chain or branched alkyl radicals, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, amyl, isoamyl or tert-amyl, heptyl, octyl, isooctyl, nonyl, decyl, undecyl, dodecyl, tetradecyl, pentadecyl or hexadecyl.

C_1-C_{16}Alkoxy is e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, amyloxy, isoamyloxy or tert-amyloxy, hexyloxy, heptyloxy, octyloxy, isooctyloxy, nonyloxy, decyloxy, undecyloxy, dodecyloxy, tetradecyloxy, pentadecyloxy or hexadecyloxy.

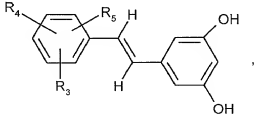
C_6-C_{10}Aryloxy is phenoxy or naphthyloxy.

Halogen is fluorine, chlorine, bromine or iodine.

The hydroxystilbenes used according to the invention can be in the form of E- or Z-isomers. They are preferably in the form of E-isomers.

Interesting compounds that are used according to the invention are dihydroxystilbenes, that is to say compounds of formula (1) wherein
R_1 and R_2 are hydroxy.

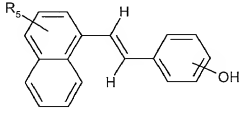
Very special preference is given to the use of compounds of formula

(2) 

,

wherein
R_3, R_4 and R_5 are as defined for formula (1), and more especially those compounds of formula (2) wherein R_3, R_4 and R_5 are hydrogen.

Also preferred are compounds of formula

(3) 

wherein
R_5 is as defined for formula (1) and is especially hydrogen.

The compounds of formula (3) are novel and the invention relates also thereto.

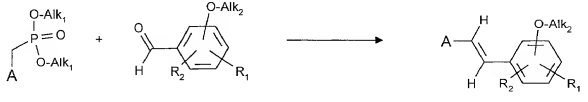
The preparation of the compounds of formula (1) is carried out in accordance with processes known *per se* by reaction of an alkyl phosphite, e.g. triethyl phosphite, with a benzyl halide, preferably benzyl bromide. The phosphonate intermediate is obtained (1st step).

The phosphonate intermediate is then reacted with an alkoxybenzaldehyde (2nd step). The subsequent dealkylation (3rd step) is carried out in accordance with customary methods.

The entire reaction sequence can be illustrated as follows:

1st step:

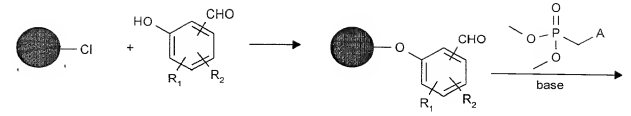
2nd step:



3rd step:

More details relating to this reaction can be found in Can. J. Chem. 48, 1554 (1970).

In a further variant, the hydroxystilbene compounds according to the invention can be prepared in a solid-phase synthesis using a trityl resin. The preparation is carried out in accordance with the following scheme:



= trityl resin radical

wherein R_1, R_2 and A are as defined for formula (1).

The method of synthesis is based on the literature procedure of R. Willard *et al.*, Chemistry & Biology, *2*, 1995, 45-51. The distinguishing feature of the preparation process according to the invention lies in the use of the trityl resin and the different method used for loading the resin.

More details relating to the preparation process according to the invention can be found in the corresponding Examples.

The hydroxystilbene compounds used according to the invention exhibit a pronounced antimicrobial action, especially against pathogenic gram-positive and gram-negative bacteria and also against bacteria of skin flora, e.g. Corynebacterium xerosis (bacteria that cause body odour), and also against yeasts and moulds. They are therefore especially suitable in the disinfection of the skin and mucosa and also of integumentary appendages (hair), more especially in the disinfection of the hands and of wounds.

They are therefore suitable as antimicrobial active ingredients and preservatives in personal care preparations, for example shampoos, bath additives, hair-care products, liquid and solid soaps (based on synthetic surfactants and salts of saturated and/or unsaturated fatty acids), lotions and creams, deodorants, other aqueous or alcoholic solutions, e.g. cleansing solutions for the skin, moist cleansing cloths, oils or powders.

The invention therefore relates also to a personal care preparation comprising at least one compound of formula (1) as well as cosmetically tolerable carriers or adjuvants.

The personal care preparation according to the invention comprises from 0.01 to 15 % by weight, preferably from 0.1 to 10 % by weight, based on the total weight of the composition, of the hydroxystilbene compound of formula (1), and cosmetically tolerable adjuvants.

Depending upon the form of the personal care preparation, it will comprise, in addition to the stilbene compound of formula (1), further constituents, for example sequestering agents, colourings, perfume oils, thickening or solidifying agents (consistency regulators), emollients, UV absorbers, skin-protective agents, antioxidants, additives that improve mechanical properties, such as dicarboxylic acids and/or Al, Zn, Ca and Mg salts of C_{14}-C_{22}fatty acids, and optionally preservatives.

The personal care preparation according to the invention may be formulated as a water-in-oil or oil-in-water emulsion, as an alcoholic or alcohol-containing formulation, as a vesicular dispersion of an ionic or non-ionic amphiphilic lipid, as a gel, a solid stick or as an aerosol formulation.

As a water-in-oil or oil-in-water emulsion, the cosmetically tolerable adjuvant contains preferably from 5 to 50 % of an oily phase, from 5 to 20 % of an emulsifier and from 30 to 90 % water. The oily phase may contain any oil suitable for cosmetic formulations, e.g. one or more hydrocarbon oils, a wax, a natural oil, a silicone oil, a fatty acid ester or a fatty alcohol. Preferred mono- or poly-ols are ethanol, isopropanol, propylene glycol, hexylene glycol, glycerol and sorbitol.

Cosmetic formulations according to the invention may be contained in a variety of cosmetic preparations. Especially the following preparations, for example, come into consideration:

- skin-care preparations, e.g. skin-washing and cleansing preparations in the form of tablet-form or liquid soaps, soapless detergents or washing pastes;
- bath preparations, e.g. liquid (foam baths, milks, shower preparations) or solid bath preparations, e.g. bath cubes and bath salts;
- skin-care preparations, e.g. skin emulsions, multi-emulsions or skin oils;
- cosmetic personal care preparations, e.g. facial make-up in the form of day creams or powder creams, face powder (loose or pressed), rouge or cream make-up, eye-care preparations, e.g. eyeshadow preparations, mascara, eyeliner, eye creams or eye-fix creams; lip-care preparations, e.g. lipsticks, lip gloss, lip contour pencils, nail-care preparations, such as nail varnish, nail varnish removers, nail hardeners or cuticle removers;
- intimate hygiene preparations, e.g. intimate washing lotions or intimate sprays;
- foot-care preparations, e.g. foot baths, foot powders, foot creams or foot balsams, special deodorants and antiperspirants or callus-removing preparations;
- light-protective preparations, such as sun milks, lotions, creams and oils, sun blocks or tropicals, pre-tanning preparations or after-sun preparations;
- skin-tanning preparations, e.g. self-tanning creams;
- depigmenting preparations, e.g. preparations for bleaching the skin or skin-lightening preparations;
- insect-repellents, e.g. insect-repellent oils, lotions, sprays or sticks;
- deodorants, such as deodorant sprays, pump-action sprays, deodorant gels, sticks or roll-ons;
- antiperspirants, e.g. antiperspirant sticks, creams or roll-ons;
- preparations for cleansing and caring for blemished skin, e.g. soapless detergents (solid or liquid), peeling or scrub preparations or peeling masks;
- hair-removal preparations in chemical form (depilation), e.g. hair-removing powders, liquid hair-removing preparations, cream- or paste-form hair-removing preparations, hair-removing preparations in gel form or aerosol foams;
- shaving preparations, e.g. shaving soap, foaming shaving creams, non-foaming shaving creams, foams and gels, preshave preparations for dry shaving, aftershaves or after-shave lotions;

- fragrance preparations, e.g. fragrances (eau de Cologne, eau de toilette, eau de parfum, parfum de toilette, perfume), perfume oils or cream perfumes;
- dental-care, denture-care and mouth-care preparations, e.g. toothpastes, gel toothpastes, tooth powders, mouthwash concentrates, anti-plaque mouthwashes, denture cleaners or denture fixatives;
- cosmetic hair-treatment preparations, e.g. hair-washing preparations in the form of shampoos and conditioners, hair-care preparations, e.g. pretreatment preparations, hair tonics, styling creams, styling gels, pomades, hair rinses, treatment packs, intensive hair treatments, hair-structuring preparations, e.g. hair-waving preparations for permanent waves (hot wave, mild wave, cold wave), hair-straightening preparations, liquid hair-setting preparations, foams, hairsprays, bleaching preparations, e.g. hydrogen peroxide solutions, lightening shampoos, bleaching creams, bleaching powders, bleaching pastes or oils, temporary, semi-permanent or permanent hair colourants, preparations containing self-oxidising dyes, or natural hair colourants, such as henna or camomile.

An antimicrobial soap has, for example, the following composition:
0.01 to 5 % by weight of the compound of formula (1)
0.3 to 1 % by weight titanium dioxide
1 to 10 % by weight stearic acid
ad 100 % soap base, e.g. the sodium salts of tallow fatty acid and coconut fatty acid or glycerol.

A shampoo has, for example, the following composition:
0.01 to 5 % by weight of the compound of formula (1)
12.0 % by weight sodium laureth-2-sulfate
4.0 % by weight cocamidopropyl betaine
3.0 % by weight NaCl and
water ad 100 %.

A deodorant has, for example, the following composition:
0.01 to 5 % by weight of the compound of formula (1)
60 % by weight ethanol
0.3 % by weight perfume oil and

water ad 100 %.

The invention relates also to an oral composition, comprising from 0.01 to 15 % by weight, based on the total weight of the composition, of the compound of formula (1), and orally tolerable adjuvants.

Example of an oral composition:
10 % by weight sorbitol
10 % by weight glycerol
15 % by weight ethanol
15 % by weight propylene glycol
0.5 % by weight sodium lauryl sulfate
0.25 % by weight sodium methylcocyl taurate
0.25 % by weight polyoxypropylene/polyoxyethylene block copolymer
0.10 % by weight peppermint flavouring
0.1 to 0.5 % by weight of a compound of formula (1) and
48.6 % by weight water.

The oral composition according to the invention may be, for example, in the form of a gel, a paste, a cream or an aqueous preparation (mouthwash).

The oral composition according to the invention may also comprise compounds that release fluoride ions which are effective against the formation of caries, for example inorganic fluoride salts, e.g. sodium, potassium, ammonium or calcium fluoride, or organic fluoride salts, e.g. amine fluorides, which are known under the trade name Olafluor.

The stilbene compounds of formula (1) used according to the invention are also suitable for the treatment of textile fibre materials. Such materials are undyed and dyed or printed fibre materials, e.g. of silk, wool, polyamide or polyurethanes, and especially cellulosic fibre materials of all kinds. Such fibre materials are, for example, natural cellulose fibres, such as cotton, linen, jute and hemp, as well as cellulose and regenerated cellulose. Preferred suitable textile fibre materials are made of cotton.

The stilbene compounds of formula (1) are also used in washing and cleaning formulations, e.g. in liquid and powder washing agents or softeners.

The stilbene compounds used according to the invention are also suitable for the treatment of plastics, especially for imparting antimicrobial properties to or preserving plastics, e.g. polyethylene, polypropylene, polyurethane, polyester, polyamide, polycarbonate, latex etc.. Fields of use therefor are, for example, floor coverings, plastics coatings, plastics container and packaging materials; kitchen and bathroom utensils (e.g. brushes, shower curtains; sponges, bathmats), latex, filter materials (air and water filters), plastics articles used in the field of medicine, e.g. dressing materials, syringes, catheters etc., so-called "medical devices", gloves and mattresses.

Paper, for example papers used for hygiene purposes, may also be provided with antimicrobial properties using the stilbene compounds according to the invention.

It is also possible for nonwovens, e.g. nappies/diapers, sanitary towels, panty liners, and cloths for hygiene and household uses, to be provided with antimicrobial properties in accordance with the invention.

The stilbene compounds can be used especially also in household and all-purpose cleaners for cleaning and disinfecting hard surfaces.

A cleaning preparation has, for example, the following composition:
0.01 to 5 % of the compound of formula (1)
3.0 % octyl alcohol 4EO
1.3 % fatty alcohol C_8-C_{10}polyglucoside
3.0 % isopropanol
ad 100 % water.

In addition to preserving cosmetic and household products, technical products, such as paper treatment liquors, printing thickeners of starch or of cellulose derivatives, surface-coatings and paints, can be preserved and provided with antimicrobial properties.

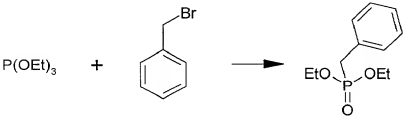
The stilbene compounds of formula (1) are also suitable for the antimicrobial treatment of wood and for the antimicrobial treatment of leather, the antimicrobial preservation of leather and the provision of leather with antimicrobial properties.

The compounds according to the invention are also suitable for the protection of cosmetic products and household products from microbial spoilage.

The following Examples serve to illustrate the invention but do not limit the invention to the Examples.

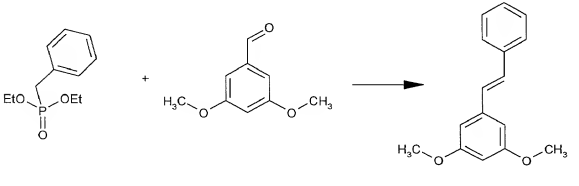
Example 1: Preparation of 3,5-dihydroxystilbene

1st step:



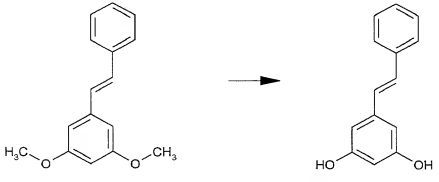
A mixture of 51.3 g (0.3 mol) of benzyl bromide and 79.1 g (0.5 mol) of triethyl phosphite is heated at 130°C until the evolution of gas has ceased (3 h). The excess of triethyl phosphite is then removed under a water-jet vacuum. The crude product can be used for the next reaction without further purification.
Yield: 60 g (0.29 mol; 96.6 % of theory)

2nd step:



16.5 g (0.3 mol) of sodium methanolate are added at 0°C to a solution of 60 g (0.29 mol) of crude diethylbenzyl phosphonate in 415 ml of anhydrous DMF. Then, at 0°C, a total of 50.0 g (0.3 mol) of 3,5-dimethoxybenzaldehyde is added in portions. After stirring for 1 hour at room temperature and heating for 1 hour under reflux, the product is precipitated by the addition of 660 ml of water/methanol (mixture ratio 2:1). Recrystallisation from water/methanol (2:1) yields 3,5-dimethoxystilbene in the form of colourless crystals.
Yield: 54.0 g (0.22 mol, 73.3 % of theory)

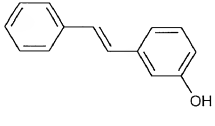
3rd step:



For demethylation, a homogeneous mixture of 54.0 g (0.22 mol) of 3,5-dimethoxystilbene and 40.0 g (0.35 mol) of pyridine hydrochloride is heated at about 165°C for 3 hours. The cooled, oily reaction mass is then introduced into 1.2 litres of 2N hydrochloric acid and the crude product is isolated by extraction with diethyl ether. Recrystallisation from toluene yields 3,5-dihydroxystilbene in the form of a pale-yellow powder.
Yield: 26.0 g (0.12 mol; 41.0 % of theory)

Example 2:

Analogously to Example 1, reaction of 20.0 g (0.12 mol) of benzyl bromide, 38.9 g (0.23 mol) of triethyl phosphite and 15.9 g (0.12 mol) of 3-methoxybenzaldehyde yields 7.0 g of 3-hydroxystilbene, corresponding to formula

(102) 

Example 3: Determination of the minimum inhibiting concentration (MIC) in the agar diffusion test

Medium:	Mueller-Hinton agar (Merck) * Sabouraud 4 % glucose agar (Merck)
Dilution medium:	sterile 0.85 % NaCl solution
Test organisms:	Staphylococcus aureus ATCC 9144 Corynebacterium xerosis ATCC 373 Escherichia coli NCTC 8196 Pseudomonas aeruginosa CIP A-22 Candida albicans ATCC 10231 * Aspergillus niger ATCC 6275
Incubation:	24 hours at 37°C * 3 days at 28°C
Test solution:	5 % stock solutions of all the test substances in a suitable solvent are prepared and diluted in serial dilutions to final concentrations of from 1000 ppm to 10 ppm.
Test principle:	0.3 ml of the dilution stage in question is mixed with 15 ml of still-liquid nutrient medium. When the nutrient substrate has solidified, 10 µl portions of the following organism dilution of the test strains in 0.85 % NaCl solution are spotted onto the agar medium:

Staphylococcus aureus ATCC 9144	1:10 dilution
Corynebacterium xerosis ATCC 373	1:100 dilution
Escherichia coli NCTC 8196	1:100 dilution
Pseudomonas aeruginosa CIP A-22	1:100 dilution
Candida albicans ATCC 10231	1:10 dilution
* Aspergillus niger ATCC 6275	1:10 dilution

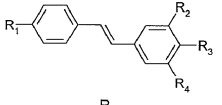
The plates are incubated at 37°C for 24 hours (A.niger 3 days at 28°C) and then the highest dilution of the test substance at which

growth is just no longer discernible (corresponds to MIC) is determined.

The results show that the test substances exhibit strong antimicrobial activity against gram-postive and gram-negative bacteria and also fungi.

The test results for the compounds listed below are given in Table 1:

General formula:



Compound of formula	R_1	R_2	R_3	R_4
(101)	H	OH	H	OH
(102)	H	OH	H	H
(103)	OH	OH	H	OH
(104)	H	H	$N(CH_3)_2$	H
(105)	OH	H	H	H
(106)	OH	H	Cl	H

Table 1:

Organisms	Compound of formula (101)[1]	Compound of formula (102)[2]	Compound of formula (103)[3]	Compound of formula (104)[4]	Compound of formula (105)[5]	Compound of formula (106)[6]
S. aureus	100	100	600	300	--	10
C. xerosis	--	--	100	--	--	--
E. coli	100	100	600	--	--	--
P. aeruginosa	1000	--	600	--	--	--
C. albicans	100	100	600	600	--	--
A. niger	100	10	--	--	10	600

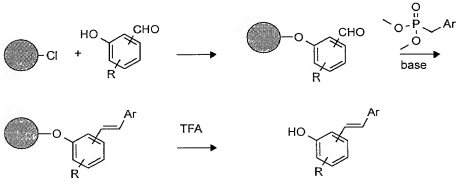
(all values MIC concentrations in ppm)

-- = not tested

Examples 4 to 87: Solid-phase synthesis method

The following hydroxystilbenes are synthesised in accordance with known procedures (R. Willard *et al.*, Chemistry & Biology, *2*, **1995**, 45-51).

The reaction is carried out in accordance with the following scheme:



[1] solution EtOH

[2] solution in DMSO

[3] solution in EtOH

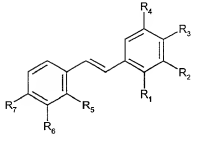
[4] solution in DMSO

[5] solution in DMSO

[6] solution in DMSO

Using this method a matrix of 12 x 7 = 84 hydroxystilbenes having the following structural scope is synthesised:

General formula:



Comp. of formula	R_1	R_2	R_3	R_4	R_5	R_6	R_7
107	H	H	OH	H	H	H	H
108	H	OH	H	H	H	H	H
109	H	OH	OMe	H	H	H	H
110	H	OEt	OH	H	H	H	H
111	H	OMe	OH	H	H	H	H
112	OH	H	OMe	H	H	H	H
113	OH	H	H	H	H	H	H
114	H	OH	OMe	OMe	H	H	H
115	H	Me	OH	Me	H	H	H
116	OH	Me	H	H	H	H	H
117	OH	H	OBzl	H	H	H	H
118	OMe	H	OH	H	H	H	H
119	H	H	OH	H	H	H	Cl
120	H	OH	H	H	H	H	Cl
121	H	OH	OMe	H	H	H	Cl
122	H	OEt	OH	H	H	H	Cl
123	H	OMe	OH	H	H	H	Cl
124	OH	H	OMe	H	H	H	Cl
125	OH	H	H	H	H	H	Cl
126	H	OH	OMe	OMe	H	H	Cl

Comp. of formula	R_1	R_2	R_3	R_4	R_5	R_6	R_7
127	H	Me	OH	Me	H	H	Cl
128	OH	Me	H	H	H	H	Cl
129	OH	H	OBzl	H	H	H	Cl
130	OMe	H	OH	H	H	H	Cl
131	H	H	OH	H	H	H	OMe
132	H	OH	H	H	H	H	OMe
133	H	OH	OMe	H	H	H	OMe
134	H	OEt	OH	H	H	H	OMe
135	H	OMe	OH	H	H	H	OMe
136	OH	H	OMe	H	H	H	OMe
137	OH	H	H	H	H	H	OMe
138	H	OH	OMe	OMe	H	H	OMe
139	H	Me	OH	Me	H	H	OMe
140	OH	Me	H	H	H	H	OMe
141	OH	H	OBzl	H	H	H	OMe
142	OMe	H	OH	H	H	H	OMe
143	H	H	OH	H	H	H	Ph
145	H	OH	H	H	H	H	Ph
146	H	OH	OMe	H	H	H	Ph
147	H	OEt	OH	H	H	H	Ph
148	H	OMe	OH	H	H	H	Ph
149	OH	H	OMe	H	H	H	Ph
150	OH	H	H	H	H	H	Ph
151	H	OH	OMe	OMe	H	H	Ph
152	H	Me	OH	Me	H	H	Ph
153	OH	Me	H	H	H	H	Ph
154	OH	H	OBzl	H	H	H	Ph
155	OMe	H	OH	H	H	H	Ph
156	H	H	OH	H			H

Comp. of formula	R_1	R_2	R_3	R_4	R_5	R_6	R_7
157	H	OH	H	H			H
158	H	OH	OMe	H			H
159	H	OEt	OH	H			H
160	H	OMe	OH	H			H
161	OH	H	OMe	H			H
162	OH	H	H	H			H
163	H	OH	OMe	OMe			H
164	H	Me	OH	Me			H
165	OH	Me	H	H			H
166	OH	H	OBzl	H			H
167	OMe	H	OH	H			H
168	H	H	OH	H	Me	H	H
169	H	OH	H	H	Me	H	H
170	H	OH	OMe	H	Me	H	H
171	H	OEt	OH	H	Me	H	H
172	H	OMe	OH	H	Me	H	H
173	OH	H	OMe	H	Me	H	H
174	OH	H	H	H	Me	H	H
175	H	OH	OMe	OMe	Me	H	H
176	H	Me	OH	Me	Me	H	H

Comp. of formula	R_1	R_2	R_3	R_4	R_5	R_6	R_7
177	OH	Me	H	H	Me	H	H
178	OH	H	OBzl	H	Me	H	H
179	OMe	H	OH	H	Me	H	H
180	H	H	OH	H	H	H	Me
181	H	OH	H	H	H	H	Me
182	H	OH	OMe	H	H	H	Me
183	H	OEt	OH	H	H	H	Me
184	H	OMe	OH	H	H	H	Me
185	OH	H	OMe	H	H	H	Me
186	OH	H	H	H	H	H	Me
187	H	OH	OMe	OMe	H	H	Me
188	H	Me	OH	Me	H	H	Me
189	OH	Me	H	H	H	H	Me
190	OH	H	OBzl	H	H	H	Me
191	OMe	H	OH	H	H	H	Me

Me = methyl
Et = ethyl
Bzl = benzyl

The microbiological data obtained are summarised in Table 2.

Table 2: MIC values in ppm for various microorganisms*)

Comp. of formula	S. heminis	E. coli	P. aeruginosa	C. albicans	A. niger
107	100	>100	>100	>100	100
108	60	30	100	30	30
109	>100	>100	>100	>100	100
110	>100	>100	>100	>100	>100
111	>100	>100	>100	>100	100
112	---	---	---	---	---

Comp. of formula	S. heminis	E. coli	P. aeruginosa	C. albicans	A. niger
113'	100	100	>100	60	60
114	>100	100	>100	>100	100
115	---	---	---	---	---
116	60	60	100	60	60
117	>100	>100	>100	>100	100
118	---	---	---	---	---
119	7.5	>100	>100	15	100
120	7.5	7.5	>100	7.5	30
121	>100	>100	>100	>100	>100
122	>100	>100	>100	>100	>100
123	>100	>100	>100	>100	100
124	15	15	>100	30	30
125	60	15	100	60	60
126	>100	>100	>100	100	100
127	---	---	---	---	---
128	>100	>100	>100	>100	100
129	---	---	---	---	---
130	---	---	---	---	---
131	>100	>100	>100	>100	>100
132	>100	>100	>100	>100	>100
133	>100	>100	>100	>100	>100
134	>100	>100	>100	>100	>100
135	>100	>100	>100	>100	>100
136	---	---	---	---	---
137	>100	100	>100	>100	>100
138	>100	>100	>100	>100	>100
139	---	---	---	---	---
140	>100	>100	>100	>100	100
141	---	---	---	---	---

Comp. of formula	S. heminis	E. coli	P. aeruginosa	C. albicans	A. niger
142	---	---	---	---	---
143	>100	>100	>100	>100	>100
145	>100	>100	>100	>100	>100
146	>100	>100	>100	>100	>100
147	>100	>100	>100	>100	>100
148	>100	>100	>100	>100	>100
149	---	---	---	---	---
150	>100	>100	>100	>100	>100
151	>100	>100	>100	>100	>100
152	---	---	---	---	---
153	>100	>100	>100	>100	>100
154	---	---	---	---	---
155	---	---	---	---	---
156	7.5	60	>100	15	30
157	7.5	15	>100	15	60
158	>100	>100	>100	>100	>100
159	>100	>100	>100	>100	100
160	>100	>100	>100	>100	100
161	---	---	---	---	---
162	7.5	30	>100	30	15
163	>100	>100	>100	>100	100
164	---	---	---	---	---
165	100	>100	>100	>100	100
166	---	---	---	---	---
167	---	---	---	---	---
168	7.5	30	100	15	30
169	30	60	100	30	30
170	>100	>100	>100	>100	>100
171	>100	>100	>100	>100	>100

Comp. of formula	S. heminis	E. coli	P. aeruginosa	C. albicans	A. niger
172	>100	>100	>100	10	>100
173	---	---	---	---	---
174	60	100	>100	60	60
175	60	60	100	60	100
176	---	---	---	---	---
177	30	60	>100	60	60
178	---	---	---	---	---
179	---	---	---	---	---
180	100	>100	>100	>100	>100
181	15	15	100	15	30
182	>100	>100	>100	>100	>100
183	>100	>100	>100	>100	>100
184	>100	>100	>100	>100	100
185	---	---	---	---	---
186	30	30	100	30	60
187	>100	>100	>100	>100	>100
188	---	---	---	---	---
189	>100	100	>100	>100	>100
190	---	---	---	---	---
191	---	---	---	---	---

--- = not determined

*) The MIC values were obtained by measuring the optical density at substance concentrations between 100; 10 and 1 ppm. In that respect some of the data are indicative values for the activity. The MIC values of the compounds having good activity were obtained by measuring the optical density at concentrations between 120; 60; 30; 15; 7.5; 3.75 ppm.

Determination of the minimum inhibiting concentration (MIC value) in microtitre plates:

Nutrient medium:

Casein/soybean flour peptone bouillon for the preparation of the precultures of the test bacteria and yeast.

Mycological slant agar for the preculture of moulds.

Examples of test organisms:

Bacteria:	Staphylococcus hominis DSM 20328
	Escherichia coli NCTC 8196
	Pseudomonas aeruginosa CIP A-22
Yeast:	Candida albicans ATCC 10231
Mould:	Aspergillus niger ATCC 6275

Procedure:

The test substances are predissolved in dimethyl sulfoxide (DMSO) and tested in a serial dilution of 1:2.

Bacteria and yeast are cultured overnight in CASO bouillon, the mould on mycological slant agar and rinsed off with 10 ml of 0.85 % sodium chloride solution (+ 0.1 % TritonX-100). All test organisms are adjusted to an organism count of 1.5×10^6 CFU/ml with 0.85 % sodium chloride solution.

The test substances are prepipetted into microtitre plates in an amount of 8 µl per well.

Previously diluted organism substances are diluted 1:100 in CASO bouillon (bacteria and yeast) and Sabouraud 2 % glucose bouillon (mould) and added to the test substances in an amount of 192 µl per well.

The test batches are incubated for 48 hours at 37°C (bacteria and yeast) or for 5 days at 28°C (mould).

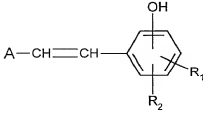
After incubation, the growth is determined by reference to the turbidity of the test batches (optical density) at 620 nm in a microplate reader.

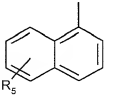
The minimum inhibiting concentration (MIC value) is the concentration of substance at which (compared with the growth control) an appreciable inhibition of the growth (≤ 20 % growth) of the test organisms is ascertained.

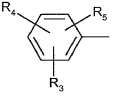
One microtitre plate is used for each test organism and substance concentration. All substances are tested in duplicate.

Patent claims

1. Use of hydroxystilbene compounds of formula

(1)  , wherein

A is a radical of formula (1a)  ; or a radical of

formula (1b)  ; and

R_1, R_2, R_3, R_4 and R_5 are each independently of the others hydrogen, halogen, hydroxy, C_1-C_{16}alkyl, C_1-C_{16}alkoxy, phenyl; C_1-C_3phenylalkyl; C_6-C_{10}aryloxy, amino, mono-C_1-C_5alkylamino, di-C_1-C_5alkylamino, or -NO_2;

in the antimicrobial treatment of surfaces.

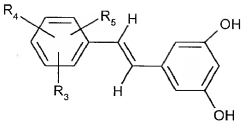
2. Use according to claim 1, wherein, in formulae (1),
R_1 and R_2 are hydroxy.

3. Use according to claim 1 or 2, wherein the compounds of formula (1) are present in the E- or Z-form.

4. Use according to claim 3, wherein the compounds of formula (1) are present in the E-form.

5. Use according to any one of claims 1 to 4, wherein there are used compounds of formula

(2)



wherein

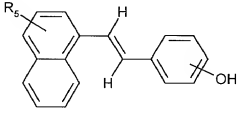
R_3, R_4 and R_5 are as defined in claim 1.

6. Use according to claim 5, wherein, in formula (2),

R_3, R_4 and R_5 are hydrogen.

7. Use according to claim 1, wherein there are used compounds of formula

(3)



wherein

R_5 is as defined for formula (1).

8. Use of the compound of formula (1) in the antimicrobial treatment, deodorisation and disinfection of the skin, mucosa and hair.

9. Use according to claim 8, wherein the compound of formula (1) is used in disinfection and deodorisation.

10. Use of the compound of formula (1) in the treatment of textile fibre materials.

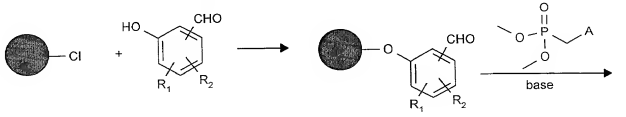
11. Use according to claim 10, wherein the compound of formula (1) is used in preservation.

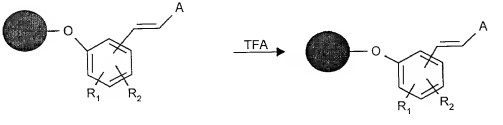
12. Use of the compound of formula (1) in washing and cleaning formulations.

13. Use of the compound of formula (1) in imparting antimicrobial properties to and preserving plastics, paper, nonwovens, wood or leather.

14. A personal care preparation, comprising
from 0.01 to 15 % by weight, based on the total weight of the composition, of the compound of formula (1), and cosmetically tolerable adjuvants.

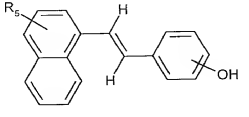
15. A process for the preparation of compounds of formula (1) according to claim 1, which process comprises preparing them in a solid-phase synthesis using a trityl resin in accordance with the following scheme:






= trityl resin radical

16. A compound of formula

(3) 

, wherein

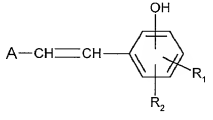
R_5 is hydrogen, halogen, hydroxy, C_1-C_{16}alkyl, C_1-C_{16}alkoxy, phenyl; C_1-C_3phenylalkyl; C_6-C_{10}aryloxy; amino; mono-C_1-C_5alkylamino; di-C_1-C_5alkylamino; or -NO_2.

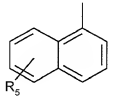
17. A compound according to claim 16, wherein

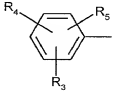
R_5 is hydrogen.

Abstract of the Disclosure

The use of hydroxystilbene compounds of formula

(1)  , wherein

A is a radical of formula (1a)  ; or a radical of

formula (1b)  ; and

R_1, R_2, R_3, R_4 and R_5 are each independently of the others hydrogen, halogen, hydroxy, C_1-C_{16}alkyl, C_1-C_{16}alkoxy, phenyl; C_1-C_3phenylalkyl; C_6-C_{10}aryloxy, amino, mono-C_1-C_5alkylamino, di-C_1-C_5alkylamino, or -NO_2;

as microbicidal active ingredients is described.

The compounds exhibit a pronounced action against pathogenic gram-positive and gram-negative bacteria, and also against yeasts and moulds. They are therefore suitable for the antimicrobial treatment, especially the preservation and disinfection, of surfaces.

US Case **HM/2-21848/US/A**

DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATIONS

☒ Original ☐ Supplemental ☐ Substitute ☒ PCT

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

HYDROXYSTILBENE COMPOUNDS USED AS MICROBICIDAL ACTIVE SUBSTANCES

which is described and claimed in:

☐ the attached specification.

☐ the specification in U.S. Application No.
filed _____ (day/month/year), and as amended on _____ (day/month/year) (if applicable).

☒ the specification in International Application No. **PCT/EP 99/07313** ✓
filed **02/10/99** ✓ (day/month/year)
assigned U.S. Application No. (if applicable), and as amended

- ☐ under PCT Article 19 on _____ (day/month/year) (if applicable)
- ☐ under PCT Article 34 on _____ (day/month/year) (if applicable)
- ☐ and further amended on _____ (day/month/year) (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information which is known by me to be material to the patentability of this application as defined in 37 C.F.R. § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119 (a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America relating to this subject matter having a filing date before that of the application on which priority is claimed:

COUNTRY/REGION (OR PCT)	APPLICATION No.	FILING DATE (day/month/year)	PRIORITY CLAIMED
Europe (designating DE)	**98811006.0**	**09/10/98**	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

I hereby claim the benefit under 35 U.S.C. § 119 (e) of any United States provisional application(s) listed below:

APPLICATION NO.	FILING DATE (day/month/year)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or PCT international application(s) designating the United States listed below and, insofar as the application discloses and claims subject matter in addition to that disclosed in the prior copending application, I acknowledge the duty to disclose all information known by me to be material to patentability as defined in 37 C.F.R. § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. APPLICATION No.	FILING DATE (day/month/year)	STATUS
		☐ Patented ☐ Pending ☐ Abandoned
		☐ Patented ☐ Pending ☐ Abandoned
		☐ Patented ☐ Pending ☐ Abandoned
		☐ Patented ☐ Pending ☐ Abandoned
		☐ Patented ☐ Pending ☐ Abandoned

PCT APPLICATION No. (designating the U.S.)	INTERNATIONAL FILING DATE (day/month/year)	U.S. APPLICATION No. (if any)	STATUS
			☐ Patented
			☐ Pending
			☐ Abandoned

I hereby appoint the following attorneys and agents, associated with Customer No. 000324, each of them with full power of substitution, revocation and appointment of associates, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Luther A. R. Hall (Reg. No. 27,337), JoAnn L. Villamizar (Reg. No. 30,598), Kevin T. Mansfield (Reg. No. 31,635), David R. Crichton (Reg. No. 37,300), Michele A. Kovaleski (Reg. No. 37,865) and Tyler A. Stevenson (Reg. No. 46,388).

Address all correspondence associated with Customer No. 000324 to ***Ciba Specialty Chemicals Corporation, Patent Department, 540 White Plains Road, P.O. Box 2005, Tarrytown, NY 10591-9005.***

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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5-00

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Full name of third joint inventor, if any

Inventor's signature _____ Date _____ (day/month/year)

Residence

Citizenship

Post Office Address same as above

Full name of fourth joint inventor, if any

Inventor's signature _____ Date _____ (day/month/year)

Residence

Citizenship

Post Office Address same as above